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Award Number: DAMD17-98-1-8539

TITLE: Determinants of Stress Fracture and Bone Mass in Elite Military Cadets

PRINCIPAL INVESTIGATOR: Felicia Cosman, M.D.

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Rensselaer, New York 12144

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Felicia Cosman, M.D.

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13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*
Longitudinal measurements of BMD indicate that some, but not all, cadets are still gaining bone mass. Gain of hip and spine bone mass in women who had regular menstrual cycles was significantly greater than then in women who had 6 or fewer cycles ($p < 0.05$). Calcium intake by female cadets was adequate ($\bar{x}$ =1200 mg/day) but calcium was not significantly related to bone loss or gain in females. In male cadets, history of high exercise and calcium intake was related to baseline bone mass and predictors of longitudinal changes are currently being evaluated. In this cohort of cadets there were 119 confirmed fractures in 79 (male =50 and female =29) cadets during the first 3 years. In a nested matched case control study (n=128) cadet blood samples were analyzed for indices of bone turnover and calcium homeostasis. There were no stress fracture related differences in these variables. Collagen I (COLI) AI genotype was analyzed on Caucasian cadets. Neither stress fracture nor bone density was related to COLIA1 genotype. Whether this gene relates to the acquisition of peak bone mass is the subject of ongoing investigation.

14. Subject Terms (keywords previously assigned to proposal abstract or terms which apply to this award)
Stress Fracture, Peak Bone Mass, Bone Mineral Density, Collagen Type I Gene

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TABLE OF CONTENTS

SECTION I - INTRODUCTION:

The study " The Determinants of Peak Bone Mass and Stress Fractures in Elite Military Cadets" was designed to examine four specific aims. They have been modified slightly because full funding for multiple phlebotomies was not granted. However, a modification to this grant was received and accepted on June 25, 2001 when $60,134 was sent based on a letter dated 2 March 2001. (Appendix A) Changes will be annotated in the text of the specific aims. In addition, bio-electrical impedance continues to be used as it has been in the data collection periods of 1999 and 2000 because of the inadequacies of BMI as a measure of fitness and fatness in cadet population. The specific aims of the study remain the same and they are:

(1) To determine the epidemiology of stress fractures in West Point Cadets during their four years at the Academy. To identify the relative importance of bone mass, quality and turnover, calcium intake and physical training in determining the risk of stress fractures.

(2) To examine the relationship of allelic variation in three separate genetic markers (Vitamin D Receptor, Type I Collagen and Estrogen receptor) to stress fractures and bone mass. NOTE: This was not initially funded but has been recently funded. In addition, some external funding was collected to complete a small analysis.

(3) To determine the incidence of abnormal gonadal function, including menstrual irregularity and sex steroid production, in male and female cadets during intensive physical training. (The procedure to research this technical objective was not funded. Women's menstrual function will still be assessed by questionnaire (Appendix B). Blood Samples were collected at baseline. There will be no assessment of male gonadal dysfunction.)

(4) To determine prospectively the relative importance of gonadal function, calcium intake and physical activity as determinants of bone turnover, mass and quality at multiple sites in male and female cadets. NOTE: The procedure to assess serum levels of sex steroids (in women: estradiol; in men: testosterone and estradiol) and the bone turnover markers (osteocalcin and crosslinked C-telopeptide) were not funded. Calcium intake will still be assessed annually by a food frequency questionnaire and physical activity will be confirmed by collecting class registration and corps squad information from the academy. Menstrual function in female cadets will be determined by questionnaire. Because the investigative team believed that the calcium homeostasis and bone turnover markers might be important as predictors of fracture risk, additional DOD funds were requested to complete these measurements using serum obtained July 1998.

SECTION II - BODY:

Background:

The determinants of peak bone mass and stress fractures are of both immediate and continuing interest to members of the military community. When higher bone mass is attained at a young age there is a subsequent reduction in the risk of osteoporosis and osteoporotic fracture later in life. The risk of stress fracture appears inversely proportional to age between 17-26 years [1-3] and may be lower in blacks than in whites. Women have more stress fractures then men. [4-6] There is also evidence that greater bone mass acquisition may reduce the incidence of both stress fractures and traumatic fracture. These factors make the acquisition of peak bone mass of great interest to the population as a whole. Therefore, stress fracture predictors and the attainment of peak bone mass are the two main areas of research being conducted on the United States Military Class of 2002.

Data Collection Efforts:

The data collection efforts during this past year focused on follow-up measurements of the different skeletal sites, stress fracture incidence, body composition data, dietary intakes and menstrual function. From May 14- June 1, 2001 data collection occurred in the cadet area of West Point. Cadets were notified by e-mail both on a group and individual basis. The cadets signed up for these appointments on the study website which allowed them to choose a time that was most convenient for them. The same instruments as in previous years were used to assess various properties of bone. The tools used for the bone densitiometry included 2 Lunar Pixi peripheral DXA machines, 1 Norland peripheral XCT 2000 scanner and a mobile Lunar DPX-IQ. The Lunar Pixi machines were used to take a calcaneus bone density measurement. The Norland pXCT provided total, trabecular and cortical density for the tibia. The DPX-IQ was used to assess the bone mineral density of the hip, femoral neck, wards triangle, trochanter, and lumbar vertebrae L2-L4. The Tanita 305 total body fat analyzer was used to assess weight, BMI, impedance, percent body fat, fat mass, lean body mass and total body water. This additional machine has been used since 1999 when the preliminary data showed that BMI alone as not a good indicator of fitness in this population. The Tanita was selected because it is easily used in a field data collection setting. Additionally, the food frequency questionnaire and the menstrual function questionnaire were provided to all cadets during their visit. (APPENDIX B and APPENDIX C).

The website (http://sql3.pica.army.mil/CadetStudy/htm), and e-mail continues to be the prime method of communication between the cadet participants and the study researchers. Additionally, it provides information to academy personnel who are interested in the study.

TABLE 1- SUMMARY OF DATA COLLECTION RESULTS

Data Collection	Baseline	1999	2000	2001
Body Composition	N/A*	767	527	394
Calcaneus	841	786	527	394
Spine Hip	292	261	211	199
Tibia	768	700	527	392
Food Frequency	786	786	527	393
Menstrual Fxn	118	92	73	88
* Body composition was not done the 1st y			BIA used since '99	

One of the primary outcomes of interest, stress fracture incidence, is being continually monitored by the orthopedics department at USMA, on the basis of initial clinical suspicion confirmed by x-ray or bone scan. One hundred and nineteen confirmed stress fractures have occurred among 79 cadets (male = 50 and female = 29) between the initiation of cadet basic training in June 1998 and March 2001. Table 2 provides a description of skeletal site for each confirmed stress fracture. These data will be continually updated with reports of more recently occurring stress fractures and confirmation of others.

TABLE 2. Skeletal Site of Confirmed Stress Fractures in Cadets thru March 2001

SITE	TOTAL
Metatarsal	64
Calcaneus	1
Tibia	36
Fibula	4
Femur	7
Clavicle	1
Metacarpal	3
Phalanges	3

SECTION 7- KEY RESEARCH ACCOMPLISHMENTS

- Maintained and updated the study website to collect data and keep study participants informed.
- Established a web page for the cadets to schedule their appointment times for the Summer of 2001
- Calcaneus bone mineral density measurements were taken on 394 in the summer of 2001
- Performed 199 spine and hip analysis in 2001 using mobile Lunar DPX-IQ scanner
- Collected 392 measurements of trabecular and cortical density of the tibia using the Norland peripheral XCT 2000 scanner in the summer of 2001.
- Collected Body Mass Index, Body Composition, Lean Body Mass and Total body water measurements on 394 cadets
- Collected menstrual function questionnaires from 88 women attending their 2001 appointments
- Collected 393 food frequency questionnaires on the during the summer of 2001
- Analyzed collagen I (COLI) A1 genotype on 626 male and 104 female cadets
- Measured the levels of PTH, BSAP, IGF-1 and NTX on a subset of cadets pending further study
- Briefed Academy personnel on 7 June 2001 on progress of the research to date
- Analyzed the relationship of stress fractures to variables of calcium homeostasis, bone turnover and IGF-1 in a nested case control design.
- Analyzed the association of collagen Type I genotype with bone mineral density and stress fracture occurrence.
- Analyzed the effects of exercise and the dietary consumption on different skeletal sites in Caucasian male and female cadets.
- Assisted USARIEM with the data collection of IGF (Protocol attached as Appendix D)
- Certified entire staff according to NIH standards on the conduct of research grants.

SECTION VIII- REPORTABLE OUTCOMES

PRESENTATIONS-

- Poster Presentation – Nieves J, Ruffing J, Zion M, Lindsay R, Cosman F Menstrual Function Predicts Change in Bone Mass in Elite Female Cadets. 22nd Annual Meeting of the American Society for Bone and Mineral Research (ASBMR) Toronto, Canada, September, 2000. (APPENDIX E)

- Nieves J, Zion M, Ruffing J, Ralston S, Uhorchak J, Gordon S, Lindsay R, Cosman F Collagen Type I Gene is not associated with BMD or Stress Fracture Occurrence in

Elite Military Cadets 23rd Annual Meeting of the American Society for Bone and Mineral Research, Poster Presentation Phoenix , AZ October 2001 (APPENDIX E)

- Cosman F, Nieves J, Zion M, Ruffing J, Uhorchak J, Gordon S, Lindsay R. Stress Fracture Occurrence is not Related to Variables of Calcium Homeostasis, Bone turnover or IGF-1 in Elite Military Cadets 23rd Annual Meeting of the American Society for Bone and Mineral Research, Poster Presentation Phoenix , AZ October 2001 (APPENDIX E)

MANUSCRIPTS-

- Nieves JW, Zion M, Ruffing J, Lindsay R, Cosman F, " Exercise and Milk Intake Are Determinants of Bone Mass In Elite Military Cadets" In Nutritional Aspects of Osteoporosis, Academic Press 2001. (APPENDIX F)

SECTION IX- CONCLUSIONS

Baseline Bone Mass

As in previous years the cadets' bone densities at the sites assessed (spine, hip, tibia and calcaneus) continue to be one standard deviation above the population mean for young adults of the cadets is high. The mean value for calcaneal BMD was 0.72 +/- 0.14 g/cm^2 in males and 0.59 +/- 0.09 g/cm^2 in females. The relationship between bone mineral density (BMD) at different sites, body mass index (BMI), fitness scores, past exercise and dietary habits and other lifestyle factors were assessed. Alcohol, tobacco, salt and caffeine consumption at baseline were not related to BMD at any skeletal site in either males or females. It is hypothesized that this could be due to the low intakes of these items or that the high level of fitness and load bearing prior to academy entrance mitigates the deleterious effect of these lifestyle factors which have been found to have an effect in other studies. Past exercise history, fitness test scores, BMI, and calcium intake were all highly correlated with BMD at different sites. Both genders also had higher than expected lumbar and total hip density with male cadets 1.28 g/cm^2 and 1.26 g/cm^2 and female cadets having 1.25 g/cm^2 and 1.13 g/cm^2 respectively. In female cadets the number of menstrual cycles prior to entering the academy was predictive of bone density in the calcaneus with women who had 9 or less than cycles the year prior to entering the academy having significantly lower density ($p < 0.05$). In men, greater exercise prior to academy entrance was predictive of greater calcaneal and tibial density, tibial mineral content, and greater cortical thickness.

Longitudinal Measures of Bone Mass:

Longitudinal measurements of BMD indicate that some, but not all, cadets are still gaining bone mass. Gain of hip and spine bone mass in women who had regular menstrual cycles was significantly greater than then in women who had 6 or fewer cycles ($p < 0.05$). Calcium intake by female cadets was adequate ($\bar{x}$ =1200 mg/day) but calcium was not significantly related to bone loss or gain in females. In male cadets, the predictors of longitudinal accrual of bone mass are currently being evaluated.

Stress Fractures:

In this cohort of cadets there were 119 confirmed fractures in 79 (male =50 and female =29) cadets during the first 3 years. In a nested matched case control study (n=128) cadet blood samples were analyzed for indices of bone turnover and calcium homeostasis. There were no stress fracture related differences in these variables. Collagen I (COLI) AI genotype was analyzed in samples from Caucasian cadets. Neither stress fracture nor bone density was related to COLIA1 genotype. Cadet blood samples are currently being analyzed for the Vitamin D receptor gene and the estrogen receptor gene. Whether any of these genes relates to the acquisition of peak bone mass is the subject of ongoing investigation.

Changes to Future Work-

The final year of data collection will be critical in assessing what happens to bone mineral density at multiple skeletal sites in this group of cadets during their four years at the academy. In May 2001, many of the cadets were away doing summer tours while we were at the academy. In order to ensure that a high proportion of the cadets who remain at the academy are evaluated, the study team will visit the academy during the winter intersession to collect data as well as during the final three weeks of school. In addition, bone density screening will be offered to cadets' parents as further incentive for the cadets to come in for their final measurement before graduation

SECTION X- REFERENCES

1. Milgrom C. Finestone A, Shlamkovitch N, Rand N, Lev B Simkin Weiner M, 1994. Youth a risk factor stress fracture: a study of 783 infantry recruits. *J Bone Joint Surg* 76B: 20-22.
2. Mori S, Burr DB.1993. Increased intracortical remodeling following fatigue damage. *Bone* 14:103-109.
3. Jones BH, Cowan DN Tomlinson JP, Robinson JR, Polly DW, Frykman PN, Epidemiology of injuries associated with physical training among young men in the army. *Med Sci Spt* 15: 197-203.

4. Schmidt-Brudvig T, T Gudger and L. Obermeier. 1983. Stress fractures in 295 trainees: A one year study of the incidence as related to age, sex and race. *Mil Med* 148:666-667
5. Reinker, K. and S Ozbourne. 1979. A comparison of male and female orthopaedic pathology in basic training. *Mil Med* 143:532-536
6. Protzman, R.R., and C. Griffis. 1977. Stress Fractures in men and women undergoing military training. *J Bone Joint Surg*

ASSISTANCE AGREEMENT

APPENDIX A

AWARD TYPE: [✓] GRANT (31 USC 6304) [ ] COOPERATIVE AGREEMENT (31 USC 6305) [ ] ER TRANSACTION (10 USC 2371)

AWARD NO: DAMD17-98-1-8539 Modification P00002	EFFECTIVE DATE See Grants Officer Signature Date Below	AWARD AMOUNT $721,766.00	Page 1 of 1 Sacelia L. Heller 301-619-7349

PROJECT TITLE:
Determinants of Stress Fracture and Bone Mass in Elite Military Cadets

CFDA 12.420

PERFORMANCE PERIOD: 15 July 1998 - 15 August 2002 (Research to be completed by 14 July 2002)	PRINCIPAL INVESTIGATOR: Felicia Cosman, M.D.
AWARDED AND ADMINISTERED BY: U.S. Army Medical Research Acquisition Activity ATTN: MCMR-AAA-A 820 Chandler St. Fort Detrick Maryland 21702-5014	PAYMENTS WILL BE MADE BY: EFT:T Army Vendor Pay DFAS-SA/FPA 1-888-478-5636 500 McCullough Avenue San Antonio, Texas 78215-2100 *(SEE PARAGRAPH TITLED "PAYMENTS" FOR INSTRUCTIONS)*
DUNS No: 002436061 TIN No:	
AWARDED TO: Health Research, Inc. One University Place Rensselaer, New York 12144	REMIT PAYMENT TO: Health Research, Inc. Controller Office One University Place Rensselaer, New York 12144-3455

ACCOUNTING AND APPROPRIATION DATA:
210204000000748119622787845954150P1FZCU0DAMD179818539FZCUP1018064 $60,134

SCOPE OF WORK:

1. Additional funds in the amount of $60,134 are hereby added to this Grant for completion of additional objectives for this study of USMA Cadets at West Point in accordance with the recipient's letter dated 2 March 2001 and revised budget dated 29 May 2001. The recipient's letter and budget are incorporated by reference.

2. If these additional objectives change/modify the human use protocol or consent form approved under this grant, the recipient is required to submit the revised documentation to the Contracting Officer for approval. Therefore, if these objectives change/modify the current protocol/consent form, the recipient is prohibited from performing this work until revised written human use protocol approval/consent form approval is received from the Contracting Officer.

Total Amount of Award: $721,766

RECIPIENT		GRANTS OFFICER	
ACCEPTED BY:		UNITED STATES OF AMERICA	
SIGNATURE		SIGNATURE	
NAME AND TITLE Annmarie Boduch Director, Sponsored Programs	DATE 5/25/01	NAME AND TITLE CHERYL R. MILES GRANTS OFFICER	DATE

USAMRAA FORM 60-R, Feb 00

MENSTRUAL FUNCTION AND BIRTH CONTROL USAGE: Summer 2001

NAME:_____

SSN: _____

BACKGROUND: Recent studies have shown that there is a correlation between different types of birth control, menstrual function and bone density therefore please take time in completing this survey.

INSTRUCTIONS: Please check the boxes that apply to you.

COW YEAR	DID YOU HAVE A PERIOD?	WHERE YOU ON BIRTH CONTROL?	WHAT TYPE OF BIRTH CONTROL?
June 2000	Yes ☐ No ☐	Yes ☐ No ☐	Oral ☐ Depoprovera ☐ Norplant ☐
July 2000	Yes ☐ No ☐	Yes ☐ No ☐	Oral ☐ Depoprovera ☐ Norplant ☐
August 2000	Yes ☐ No ☐	Yes ☐ No ☐	Oral ☐ Depoprovera ☐ Norplant ☐
September 2000	Yes ☐ No ☐	Yes ☐ No ☐	Oral ☐ Depoprovera ☐ Norplant ☐
October 2000	Yes ☐ No ☐	Yes ☐ No ☐	Oral ☐ Depoprovera ☐ Norplant ☐
November 2000	Yes ☐ No ☐	Yes ☐ No ☐	Oral ☐ Depoprovera ☐ Norplant ☐
December 2000	Yes ☐ No ☐	Yes ☐ No ☐	Oral ☐ Depoprovera ☐ Norplant ☐
January 2001	Yes ☐ No ☐	Yes ☐ No ☐	Oral ☐ Depoprovera ☐ Norplant ☐
February 2001	Yes ☐ No ☐	Yes ☐ No ☐	Oral ☐ Depoprovera ☐ Norplant ☐
March 2001	Yes ☐ No ☐	Yes ☐ No ☐	Oral ☐ Depoprovera ☐ Norplant ☐
April 2001	Yes ☐ No ☐	Yes ☐ No ☐	Oral ☐ Depoprovera ☐ Norplant ☐
May 2001	Yes ☐ No ☐	Yes ☐ No ☐	Oral ☐ Depoprovera ☐ Norplant ☐

1. If you were on birth control prior to entering the academy which type was it?

Oral ☐ Depoprovera ☐ Norplant ☐

APPENDIX C

FOOD FREQUENCY QUESTIONAIRE: SUMMER 01

NAME:_____
SSN:_____

Instructions: Please think about the foods you regularly ate over the past year, what size servings you ate, and how often you ate them. Then fill in the appropriate boxes. If you ate two medium bowls of cereal a day you would fill in the boxes like this:

EXAMPLE:

		Serving Size			Frequency			
BREAKFAST	**Medium Serving Size**	S	M	L	No. of Servings	Per day	Per week	Per month
Cereal with Milk	1 med bowl	☐	☑	☐	2	☑	☐	☐

START HERE:

		Serving Size			Frequency			
DAIRY	**Medium Serving Size**	S	M	L	No. Of Servings	Per Day	Per Week	Per Month
Cottage cheese	½ cup	☐	☐	☐		☐	☐	☐
cheese	2oz or 2 slices	☐	☐	☐		☐	☐	☐
yogurt	1 cup	☐	☐	☐		☐	☐	☐
tofu	2 oz	☐	☐	☐		☐	☐	☐
BREAKFAST								
Cereal with Milk	1 med bowl	☐	☐	☐		☐	☐	☐
LUNCH								
Cheese dishes, such as macaroni and cheese	1 cup	☐	☐	☐		☐	☐	☐
Pizza/lasagna	2 slices	☐	☐	☐		☐	☐	☐
SWEETS								
Ice Cream or frozen yogurt	1 scoop ½ cup	☐	☐	☐		☐	☐	☐
VEGETABLES								
Mustard or turnip greens or collards	½ cup	☐	☐	☐		☐	☐	☐
Beans including pinto, kidney, baked or black eye peas	¾ cup	☐	☐	☐		☐	☐	☐
Broccoli or kale	½ cup	☐	☐	☐		☐	☐	☐
BEVERAGES								
Glass of milk	8 oz	☐	☐	☐		☐	☐	☐
Coffee/Tea (caffienated)	1 cup	☐	☐	☐		☐	☐	☐
Cola Product (caffienated diet or reg)	12 oz (1 can)	☐	☐	☐		☐	☐	☐

To how many meals per day do you add salt? (circle the correct answer)

0 1 2 3 meals a day

Do you take any vitamin or nutritional supplements? Yes No

If yes, what is the name of your vitamin or nutritional supplement?_____

Do you take a calcium supplement or is calcium contained in your vitamin supplement? Yes No

TITLE: Relationship between bioassayable human growth hormone and bone mineral content in male and female service members.

Principal Investigator: Michael J. Durkot, Ph.D.
Senior Project Officers: CPT Bradley C. Nindl, Ph.D. and COL Charles R. Scoville, M.P.T.
Co-Investigators: LTC Kathleen M. Sheehan, M.D., MAJ William J. Fall, DVM, COL John Uhorchak, Jeri Nieves, Ph.D., and Felicia Cosman, M.D.

I. NON-TECHNICAL SYNOPSIS:

Achieving and maintaining optimal bone health for service members is necessary for reaching a high level of military readiness. Stress fractures impose a significant financial burden on the military by delaying the training of new recruits. Stress fractures increase the length of training time, program costs, and time to military readiness. Additionally, stress fractures, a short-term risk, may share their etiology with long-term risk of osteoporosis (*Reducing stress fracture in physically active military women*, National Academy Press, Washington, D.C., 1998). While the mechanisms underlying the development of skeletal mass are many, *it is firmly grounded in the endocrinological system*. In particular, **growth hormone** positively impacts (via insulin-like growth-factor-1) processes for bone growth and remodeling. In fact, growth hormone administration has proven to be an efficacious intervention for osteoporosis. A provocative hypothesis is that impaired pituitary release of human growth hormone may be in part responsible for defects in skeletal mass. If this hypothesis is accurate, it would prove beneficial to screen people who may have impaired growth hormone function and hence be at risk for reduced bone mass and skeletal-related pathologies.

The traditional means of measuring serum growth hormone is by radioimmunoassay. However, there is controversy on what a RIA actually measures and the subsequent clinical utility of its interpretation. More meaningful information concerning the relative physiological importance of endogenous growth hormone may be through its assessment by bioassay. The conventional method of assessing "bioactivity" of GH (BGH) is the *in vivo* hypox rat tibial assay first reported by Greenspan et al. in 1949 (4). The Department of Defense may benefit from this screening method targeted at identifying soldiers predisposed to skeletal pathologies (i.e. stress fractures and later osteoporosis). For this to be practical, viable "biomarkers" that relate to bone health must first be established. This study will 1) use an *in vivo* bioassay to measure the impact that human growth hormone of male and female service members has on the rat epiphysial growth plate, and 2) correlate this information to DEXA measures of bone mineral content in the same male and female service members. By establishing a link between BGH and bone mineral content, mechanistic insight on bone modeling can potentially be gathered and used to target interventions (i.e. either exercise training or pharmacalogical) that would increase BGH leading to a greater level of bone health. We expect that BGH will show a stronger positive relationship with bone mineral density than immunoreactive growth hormone (IGH).

SA336

Menstrual Function Predicts Change in Bone Mass in Elite Female Cadets. J. Nieves, J. Ruffing,* M. Zion,* R. Lindsay, F. Cosman. Clinical Research Center, Helen Hayes Hospital, West Haverstraw, NY, USA.

As few studies have prospectively evaluated longitudinal changes in bone mass in females with exercise induced amenorrhea, a sample of 73 female cadets (average age 19) entering the United States Military Academy (USMA) had bone density assessments at baseline and after one year. The relative importance of menstrual function and calcium intake on the peak mass accrual at various skeletal sites was evaluated. Menstrual function and calcium intake were assessed prospectively by questionnaire during the year. Menstrual function was defined as regular (≥10 menstrual cycles/year); mild oligomenorrhea (7-9 cycles per year) and oligomenorrhea/ amenorrhea (6 or fewer cycles per year). A Lunar DPX-IQ Dual x-ray absorptiometry (DXA) was used to assess bone mineral density (BMD) at the lumbar spine and total hip. On average these female cadets had spine and hip BMD values that were one standard deviation above the manufacturers young normal reference population. Women who had regular menstrual cycles during the year gained bone in the spine and total hip (+0.020 gm/cm^2 and +0.014 gm/cm^2 respectively) as compared to women who had oligomenorrhea/ amenorrhea (fewer than 6 menstrual cycles per year) who lost spinal and hip bone mass (-0.012 gm/cm^2 and -0.014 gm/cm^2 respectively; p-value<0.05 versus regular menstrual cycles). Women in the mild oligomenorrhea category gained bone in the spine (+0.020 gm/cm^2) and had an insignificant change in the total hip (+0.005 gm/cm^2), a change intermediate to the two extreme categories of menstrual function. In the group of women (n=49) who had regular menstrual cycles, there was no significant difference in change in spine or hip BMD between women using oral contraceptives and women with naturally occurring regular menses. On average, female cadets in each category of menstrual function had calcium intakes that were at or above the levels recommended (mean intake of 1200 mg/day). Calcium intake was not independently related to bone loss or gain in this population of women. Other differences in bone mass accrual may relate to physical activity level, which is currently being assessed in this population. Consistent with what has been seen in retrospective studies of elite athletes; normal menstrual function is a major determinant of bone gain in the spine and hip.

SA337

Increased Turnover and Loss of Bone Mass Following Castration in Male Rabbits. C. E. Hotchkiss. Pathology/Comparative Medicine, Wake Forest University School of Medicine, Winston-Salem, NC, USA.

While the importance of estrogen in maintenance of bone mass in women is well-understood, less is known about the role of gonadal hormones in the development of male osteoporosis. The effect of castration on bone in male rabbits, an animal model whose bone undergoes intracortical Haversian remodeling, was studied. Ten 1-year-old male New Zealand White rabbits were obtained from a commercial supplier. Five were castrated, while the other five underwent sham surgery. The rabbits were sacrificed 3 months after surgery, and bones were collected for future histomorphometric evaluation. Densitometry (pQCT) was performed at baseline and just prior to necropsy. Urine was collected at necropsy, and serum was collected at baseline, 8 weeks, and at necropsy to evaluate markers of bone turnover. Radiography performed at 6 weeks following surgery showed that approximately half of all the growth plates at the distal radius and ulna were closed in these animals. Two sites were evaluated by pQCT (Norland/Stratec X3000A) *in vivo*; the midshaft femur and LV4. Positioning for the midshaft femur in the live animal was not ideal, so this bone was also scanned *ex vivo* to obtain data with less variability. Castration decreased bone mass overall, and particularly affected the cortical bone. The cortical thickness of the femur was significantly lower in castrated rabbits compared to sham-operated rabbits (1.52 ± 0.04 mm vs. 1.68 ± 0.05 mm). The total BMD of LV4 was significantly lower in castrated rabbits (519 ± 24 mg/ml vs. 562 ± 16 mg/ml), and the difference could be accounted for by differences in the cortical/endocortical compartment (566 ± 21 mg/ml vs 634 ± 13 mg/ml). Following an ether extraction to remove rabbit serum proteins, a commercial ELISA (ALPCO) was used to measure testosterone. As expected, castration significantly reduced testosterone (0.21 ± 0.03 ng/ml vs. 2.97 ± 0.92 ng/ml). Urinary pyridinoline was measured by ELISA (Pyrilinks, Metra Biosystems), and was significantly higher in castrated than in sham-operated rabbits (123 ± 29 nmol/mmol Cr vs. 58 ± 12 nmol/mmol Cr). There was a significantly higher osteocalcin (Novocalcin, Metra Biosystems) in orchiectomized rabbits by three months (35 ± 3 ng/ml vs. 27 ± 2 ng/ml), although this difference was due to a decrease in the sham-operated rabbits over time, rather than an increase in the orchiectomized animals. Serum was assayed for IGF-1 by ELISA (Active™ Rat IGF-1 EIA, DSL, Inc.). By three months, values for ORX rabbits were significantly higher than for SHAM rabbits (167 ± 49 µg/ml vs. 37 ± 7 µg/ml). Serum calcium and phosphorus were measured using standard techniques, and PTH using an ELISA (ALPCO). There were no intergroup differences in these parameters. In conclusion, castration increases bone turnover in male rabbits, resulting in a decrease in bone mass.

SA338

Compared Trabecular Bone Architecture in Men and Women. E. R. Legrand,[1] D. Chappard,[2] I. Degasne,*[1] M. Basle,*[2] M. Audran.[1] [1]Rheumatology, CHU , Angers, France. [2]Histology, CHU , Angers, France.

We have shown that trabecular bone connectivity is a major and independant determinant of vertebral fracture in men with mild osteoporosis (OP) (1). The purpose of the present study was to compare trabecular bone microarchitecture in osteoporotic men and women.

Spine and hip bone density (BMD) and transilliac bone biopsy were obtained in 31 male patients with idiopathic OP(I-OP), 10 male patients with hypogonadism induced-OP (H-OP) and 29 women with postmenopausal OP. Histomorphometric analysis was done on a Leica quantimet image processor and the followings measures were performed : trabecular bone volume (BV/TV), trabecular thickness (Tb Th) and number (Tb N), Interconnectivity Index (ICI), Star Volume of the bone marrow, Characterization of the trabecular network (node and free-end count).

Results (1) Spine and Hip BMD were significantly lower in women (0.64 et 0.63 gr/cm2) than in men with I-OP (0.73 and 0.71 gr/cm2) or G-OP (0.70 and 0.70 gr/cm2)

(2) There were no significant difference between postmenopausal women and men with I-OP for BV/TV, Tb.Th and all architectural parameters (TbN, ICI, Star, Free-end count and Node count)

(3) In contrast TbN and Node count were significantly lower whereas ICI, Free-end count were higher in men With H-OP

These results show that (1) despite a higher BMD, architectural changes are equivalent in men with idiopathic OP and women with post menopausal osteoporosis; (2) trabecular bone microarchitecture seems to be profoundly altered in men with hypogonadism-induced OP.

(1) E Legrand et al. Trabecular bone microarchitecture, bone mineral density and vertebral fractures in male osteoporosis. J Bone Miner Res 2000; 15: 13-19.

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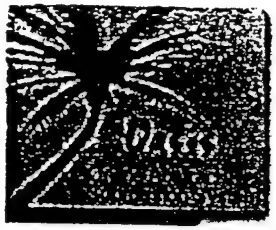
Men with Prostate Cancer Treated with GnRH Agonists Lose Bone. S. A. Stoch,[1] R. A. Parker,*[2] G. Bubley,*[1] L. Chen,*[2] C. J. Doyle,*[3] A. Vincelette,*[1] S. L. Greenspan.[4] [1]Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA, [2]Biometrics Center, Beth Israel Deaconess Medical Center, Boston, MA, USA, [3]Urology, Harvard Vanguard , Boston, MA, USA. [4]Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA.

Prostate cancer is the second leading cause of cancer in men. Treatment with GnRH agonists (GnRH-a) results in hypogonadism. To determine the impact of GnRH-a therapy in men with prostate cancer, we compared bone mineral density (BMD) [AP and lateral spine, total hip, femoral neck, trochanter, wrist and total body], heel ultrasound, and markers of bone turnover in men with prostate cancer with ≥ 6 months of treatment (N=19, age 73± 6 years, duration of treatment 40.5± 31.7 months) to men without GnRH-a treatment (N=41, age 70± 9 years). In addition, we examined BMD parameters in healthy controls, (N=197, age 66± 10 years) to determine the potential impact of prostate cancer on bone mass. Results: mean ± SD

BMD (g/cm^2)	GnRH-a Pos	GnRH-a Neg	Controls
PA Spine	1.04± 0.21	1.12± 0.21	1.11± 0.19
Lateral Spine	0.69± 0.17**	0.83± 0.20	0.81± 0.15
Total Hip	0.94± 0.14*	1.05± 0.16	1.01± 0.13
Femoral Neck	0.75± 0.12	0.82± 0.15	0.81± 0.12
Trochanter	0.73± 0.14*	0.82± 0.15	0.79± 0.12
Radius (1/3)	0.67± 0.11**	0.78± 0.07	0.77± 0.07
Total Body	1.13± 0.13**	1.27± 0.14	
Heel U/S	0.51± 0.27**	0.59± 0.17	0.56± 0.14
Urine NTX	78.21± 47.95**	35.97± 19.95	
BSAP	36.43± 28.69**	21.99± 6.53	
Osteocalcin	10.86± 5.81	8.83± 4.57	

* P<0.05, **P<0.01 with GnRH-a vs. without GnRH-a

Lateral spine, total hip, trochanter, radius, whole body and heel ultrasound are all significantly lower in hypogonadal men treated with GnRH agonist therapy than in eugonadal men with prostate cancer. There were no differences in the BMD of the eugonadal men and control groups. Urine NTX (BCE/creat), a marker of bone resorption and BSAP (U/l), a marker of bone formation were both significantly higher in the hypogonadal men consistent with an increase in bone turnover. We conclude that treatment with GnRH agonists in



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Collagen TypeI Gene Is Not Associated With BMD or Stress Fracture Occurence in Elite Military Cadets

J. W. Nieves,[1] M. Zion,*[1] J. Ruffing,*[1] S. Ralston,[2] J. M. Uhorchak,*[3] S. Gordon,*[1] R. Lindsay,[1] F. Cosman.[1] [1]Clinical Research Center, Helen Hayes Hospital, West Haverstraw, NY, USA, [2]University of Aberdeen Medical School, Aberdeen, United Kingdom, [3]Keller Army Hospital, West Point, NY, USA.

A polymorphism affecting the Sp1 binding site in the collagen I (COLI) A1 gene has been associated with fracture and central bone density in some but not all cohorts of women and men. COLIA1 genotypes were analyzed in relation to bone density (at average age 18), markers of bone turnover, and stress fracture occurrence in a cohort of 730 Caucasian military cadets (626 male and 104 female) from the United States Military Academy at West Point. COLIA1 genotype was

determined by polymerase chain reaction analysis of genomic DNA extracted from peripheral blood leukocytes. Markers of bone turnover in serum were measured by RIA for BGP, IRMA for BSAP, and ELISA for NTX. Bone density was measured at the calcaneus by Lunar PIXI and at the tibia by peripheral-QCT (Stratec/Norland). Stress fractures occurred in 62 cadets (male=40; female=22) in this sample over a 2.5-year period. These were diagnosed by an orthopedic surgeon and confirmed by x-ray or scintiscan. On analysis of genotype distribution in the entire study group we found 64% SS homozygotes, 32% Ss heterozygotes, and 4% ss homozygotes, similar results to those previously reported in other Caucasian populations. In both males and females, age, weight, height and body mass index were similar across the three genotypes. Between group comparisons by ANOVA showed that COLIA1 genotype was not significantly associated with BMD at the calcaneus or tibia or with tibial cortical thickness. COLIA1 was not associated with markers of bone turnover (NTX, BSAP, BGP) in this cohort of military cadets. In addition, stress fracture incidence in males or females was not associated with COLIA1 genotype. We conclude that COLIA1 does not appear to be an important determinant of bone density or susceptibility to stress fractures in this young healthy population. Whether this gene relates to the acquisition of peak bone mass is the subject of an ongoing longitudinal investigation in this cohort.

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Stress Fracture Occurrence is not Related to Variables of Calcium Homeostasis, Bone Turnover, or IGF-1 in Elite Military Cadets

F. Cosman,[*] J. Nieves,[1] M. Zion,[*1] J. Ruffing,[*1] J. Uhorchak,[*2] S. Gordon,[*1] R. Lindsay.[1] [1]Clinical Research Center, Helen Hayes Hospital, West Haverstraw, NY, USA, [2]Keller Army Hospital, West Point, NY, USA.

The etiology and pathophysiology of stress fractures in young adults

may differ from that of other types of fractures including those related to osteoporosis. In some populations, low levels of vitamin D, and IGF-1 and high levels of PTH and bone turnover indices increase the risk of fracture occurrence. Our objective was to determine whether a relationship could be found between blood levels of these indices and stress fracture in a population of Caucasian military cadets from an ongoing study of the class entering the USMA at West Point in 1998 (initial n=758.) Over 2.5 years, stress fracture occurrence was diagnosed by standard orthopedic procedures (bony tenderness and swelling with bone, cortical or periosteal abnormality found on x-ray or increased uptake on scan). A total of 64 cadets had one or more confirmed stress fractures (25 females and 39 males) and they were matched for gender and age ? 6 months with cadets who had no bony injury. 2 non-fractured cadets were compared with every 1 fracture case for this nested case/control study. Blood samples were obtained upon cadet entry to USMA and serum samples were stored in separate aliquots and frozen at -70°. Intact PTH, BSAP and IGF-1 were measured by IRMA, 25(0H)D by radioceptor assay, and NTx by Elisa. Mean levels of PTH, 25(0H)D and IGF-1 were all in the normal range with no gender or fracture case-related differences. Levels of bone turnover, particularly bone formation, were higher in males than females but, again, there were no differences between fracture cases and controls. These results indicate that stress fracture incidence in military cadets does not appear to be related to prospective measurement of PTH, 250HD, IGF-1, or bone turnover indices.

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CHAPTER 12

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Exercise and Milk Intake Are Determinants of Bone Mass in Elite Military Cadets

I. Abstract

Peak bone mass is clearly related to genetic and lifestyle factors. A sample of 557 male cadets entering the U.S. Military Academy (USMA) had multiple bone density assessments to determine the relative importance of milk intake and physical activity on bone mass at various skeletal sites. Dietary intakes of calcium, salt, and caffeine, and physical activity over the year preceding entry to the USMA were assessed by written questionnaire. Calcium intake was almost solely determined by milk intake in this population. A Lunar DPX-IQ dual energy X-ray absorptiometry (DXA) instrument was used to assess bone density (BMD) at the lumbar spine and total hip in a randomly chosen subset of 131 male cadets. A peripheral DXA instrument (Lunar) was used to assess heel BMD in 557 male cadets and peripheral pQCT (quantitative computerized tomography equipment) (Norland) was used to measure tibial bone content and cortical thickness in 503 male cadets. On average,

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the cadets had spine, hip, and heel BMD values that were one standard deviation above the manufacturers' young normal reference population. Higher milk intakes (3 glasses/day or more) were significantly related to greater total tibial content ($p = 0.01$), cortical thickness ($p = 0.02$), and heel BMD ($p = 0.05$). There was also a trend toward higher BMD of the spine and hip in those with higher milk intakes. In male cadets, intense physical activity in the past year (exceeding 12 h/week) was associated with significantly higher bone mass throughout the skeleton including the spine, hip, heel, and tibia (3 and 6% higher; all $p < 0.02$) in comparison to cadets with less intense levels of physical activity. Salt and caffeine were not associated with bone mass. In conclusion, males with bone mass at the high end of normal can still maximize bone mass at all skeletal sites by high levels of exercise and adequate calcium intake through milk consumption.

II. Introduction

Peak bone mass, under normal pubertal conditions, is clearly related to genetic and lifestyle factors, including exercise and dietary calcium intake. Although there have been numerous studies looking at the determinants of peak bone mass in females, there are far fewer studies that have focused on males. Calcium intake, often assessed as milk intake, has been related to bone mass in several studies [1–4]. Exercise has also been found to increase peak bone mass [5–7]. A possible interaction between exercise and calcium intake was reported in 1996 [8].

Males have routinely been reported to have higher peak bone mass than females, and this discrepancy may result in higher rates of stress fractures in females than in males [9,10].

III. Methods

All cadets in the class of 2002 at the U.S. Military Academy (USMA) in West Point, New York, were asked to participate in a longitudinal study to evaluate the determinants of peak bone mass and stress fractures in elite military cadets over a 4-year period. A total of 891 cadets consented to this study: 752 males and 139 females of various racial backgrounds.

In this analysis we restricted the study population to 583 Caucasian males in the USMA class of 2002. The mean (SD) age in years was 18.9 (1.09), the average height in centimeters was 178.3 (7.0), and the weight in kilograms was 78.3 (13.2).

Information on lifestyle variables for the one-year period prior to entry into the academy was collected at baseline, including the levels of physical activity (h/week) and amount of milk intake (glasses/day).

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Baseline bone density measurements were made using the Lunar pDXA (PIXI) for the calcaneus (n = 583) and using the Norland pQCT at the distal tibia (n = 527). A randomly selected subset (n = 135) had measurements of spine and hip BMD by Lunar DPX-IQ.

IV. Results

Table I provides data on the distribution of cadets into each category of physical activity and milk intake. Baseline bone measures at each skeletal site were approximately one standard deviation above young normal at the calcaneus and total hip (Table II).

The difference in spine and total hip bone density between cadets at each level of exercise was 8 and 12%, respectively, between the males with high and low levels of exercise reported in the year prior to entering the USMA. These results should be viewed with caution because of the small number of cadets in the low exercise group. However, calcaneus BMD measurements in 583 cadets also showed a 6% higher BMD (0.5 SD) in cadets with a history of 11+ h/week of exercise vs 1–3 h/week.

Higher levels of prior exercise led to increases in tibial density and mineral content. There was a large gradient in the difference in tibia mineral content between those with a history of high and low exercise (13%) and a more modest difference in tibial density (6%) between exercise categories. The cortical thickness is also larger by about 12% in cadets in the high exercise group, a difference attributable in part to a significant increase in periosteal apposition with increasing levels of exercise.

The male cadets with low milk intake (<1 glass/day) had 4% lower spine BMD and 6% lower hip BMD than those drinking 3 or more glasses

TABLE I Baseline Levels of Physical Activity and Milk Intake

Variable	*Number of cadets*
Level of physical activity, h/week	
1–3	30
4–6	116
7–10	165
≥ 11	262
Milk intake, glasses/day	
< 1	124
1–2	267
≥ 3	182

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TABLE II Baseline Bone Density at Each Skeletal Site

Site	*Mean ± SD*	*(Range)*
Calcaneus, gm/cm^2	0.71 ± 0.13	(0.44–1.27)
Lumbar spine, gm/cm^2	1.28 ± 0.13	(0.98–1.65)
Total hip, gm/cm^2	1.26 ± 0.13	(0.96–1.68)
Femoral neck, gm/cm^2	1.24 ± 0.13	(0.92–1.62)
Tibial density, mg/cm^3	815 ± 78.6	(611–1017)
Mineral content, mg/mm	356 ± 44.5	(227–482)
Cortical thickness, mm	6.23 ± 0.74	(4.53–8.21)
Periosteal circumference, mm	73.4 ± 5.3	(56.0–97.5)

a day. The difference in calcaneus BMD by milk drinking was 6% between the high and low milk intakes.

Tibial mineral content and density were 4–6% higher in those with high milk intake than in those with low milk intake. Cortical thickness was greater in those with high milk intakes; this was a result of a small nonsignificant increase in periosteal circumference as well as a decrease in endosteal circumference. The combined effect of exercise and milk intake on cortical thickness was evaluated. As exercise increases, the cortical thickness increases, except in the group with low milk intake. As calcium intake goes up, cortical thickness goes up, although at the highest level of exercise there is little difference between the two higher intakes of milk.

V. Discussion

Male cadets with low calcium intakes (<1 glass of milk a day) had lower bone density of the hip and calcaneus than cadets with higher milk intakes. Furthermore, male cadets with high milk intakes have higher tibial mineral content, greater density, and greater cortical thickness.

Male cadets who had exercised at least 7 h/week had greater bone density at the hip and calcaneus than cadets who exercised less than 3 h/week. In addition, exercise led to greater tibial mineral content, density, and cortical thickness, in part through a significant increase in periosteal apposition.

There were some limitations to this study. Time constraints prevented the acquisition of extensive dietary data, and therefore we could not control for total caloric intake. In addition, it is noted that selection bias may lead the persons with higher bone mass to select more strenuous levels of physical activity.

In conclusion, exercising at least 7 h/week and drinking more than one

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glass of milk a day independently increase bone density at various skeletal sites in young men.

Acknowledgment

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